The long-term fate of epistaxis patients with exposure to antithrombotic medication

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Abstract: The goal of this study was to evaluate independent risk factors for long-term epistaxis recurrences and their severity. Individual retrospective cohort study-2b level of evidence. The medical information of 603 emergency epistaxis patients was acquired during a former study. This cohort has been contacted 6 years later by conventional mail and asked to answer a specific paper questionnaire. The following parameters were evaluated: recurrent epistaxis episodes, need for a surgical intervention to stop the recurrent bleeding, patient's history for hypertension and diabetes, intake of hemostasis impairing medication now and in the past. One hundred and six (106) patients were included in the study (35.8 % response rate). The mean observation period was 76.58 months. Almost half of the patients (41.5 % = 44/106) reported at least one recurrent epistaxis episode. Patients with exposure to VKA (vitamin K antagonists) showed significantly more frequently a recurrent epistaxis episode. The binary logistic regression confirmed the intake of VKA as an independent and significant risk factor with an odds ratio of 11.6. Every single patient who had to undergo a surgical intervention to stop a recurrent bleeding stated ASA (Acetylsalicylic Acid) intake. We provide evidence that the intake of a vitamin K antagonist is an independent long-term risk factor for recurrent epistaxis episodes. The intake of ASA is a risk factor for the severity of recurrent epistaxis with the increased need for a surgical intervention not only in a short- but also in a long-term perspective. Level of evidence: This prognostic investigation, designed as a combined prospective and retrospective cohort study, reaches level 2b level of evidence as it includes retrospective aspects.

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Abstract:

Objectives/Hypothesis

The goal of this study was to evaluate independent risk factors for long-term epistaxis recurrences and their severity.

Study design

Individual retrospective cohort study - 2b level of evidence.

Methods

The medical information of 603 emergency epistaxis patients was acquired during a former study. This cohort has been contacted six years later by conventional mail and asked to answer a specific paper-questionnaire. The following parameters were evaluated: Recurrent epistaxis episodes, need for a surgical intervention in order to stop the recurrent bleeding, patient's history for hypertension and diabetes, intake of hemostasis impairing medication now and in the past.

Results

One hundred and six (106) patients were included in the study (35.8% response rate). The mean observation period was 76.58 months. Almost half of the patients (41.5%=44/106) reported at least one recurrent epistaxis episode. Patients with exposure to VKA (vitamin K antagonists) showed significantly more frequently a recurrent epistaxis episode. The binary logistic regression confirmed the intake of VKA as an independent and significant risk factor with an odds ratio of 11.6. Every single patient who had to undergo a surgical intervention in order to stop a recurrent bleeding stated ASA (Acetylsalicylic Acid) intake.

Conclusion

We provide evidence that the intake of a vitamin K antagonist is an independent long-term risk factor for recurrent epistaxis episodes.

The intake of ASA is a risk factor for the severity of recurrent epistaxis with the increased need for a surgical intervention not only in a short- but also in a long-term perspective.

Key-Words:

Epistaxis, Nose bleed, Recurrence, Risk Factors, Prognosis, Prevalence, Warfarin, ASA, Aspirin, Acetylsalicylic Acid

Level of Evidence:

This prognostic investigation, designed as a combined prospective and retrospective cohort study, reaches level 2b level of evidence as it includes retrospective aspects.

Introduction:

Epistaxis is a leading cause for admission to the otorhinolaryngologic emergency room. The majority of the population will suffer a nosebleed at some point in their life. Epidemiologic surveys showed an adult life prevalence of 60 percent for an epistaxis episode. Only every tenth case seeks medical attention.[1]

Besides the idiopathic episodes, where the cause remains unclear, the etiology can either be local or systemic. Concerning systemic etiologies, one must be aware of iatrogenic influences on the hematologic equilibrium through medication exposure. First and foremost important hemostasis impairing medications like vitamin K antagonists or antiplatelet drugs interfere with this system. Hemorrhagic side effects of oral anticoagulation or antiplatelet drugs seem intuitively apparent regarding their pharmacological characteristics and goals.[2] Patients on such medication walk a tightrope between reducing the risk for thrombotic events and the inevitable risk of bleeding.

On a daily basis, we are often confronted with epistaxis patients' concerns about their course of any following bleeding episodes in the future, not only inquiring about the moment but also the following years.

It is important to be able to define independent risk factors and evaluate their presence in order to give the patient an adequate and customized prediction. For this purpose, the exact acquirement of a patient's history is once again of utmost importance.

Several epistaxis risk factors have been investigated and discussed controversially for many years, i.e. physical and chemical irritation, temperature and humidity,

hypertension, septal pathologies and inflammatory conditions. Some proposed factors were able to maintain their position and others were pushed into the background. In recent years, anticoagulative and antiaggregative medication, traumatic injury, alcohol consumption, hematologic disorders and long lasting hypertension/arteriosclerosis could maintain their position in being relevant risks for nasal bleeding. [5,6,7,8,9]

However, the impact of independent risk factors after an epistaxis episode in a long-term perspective is largely unknown.

Based on a study of our clinic that investigated risk factors within epistaxis patients presenting at the ENT (Ear, Nose and Throat) emergency[3], we designed a long-term follow-up survey study.

The goal of this study was to evaluate, whether certain independent factors could help to predict any recurrences and their severity on the basis of long-term survey data.

Materials and Methods:

This investigation was designed as a cohort survey study at the University Hospital of Zurich. During a former study we systematically collected medical information of 603 emergency epistaxis patients who have been seen and treated at the unit (including in hospital therapy and outpatient treatment) of our tertiary ENT department.[3] The treating physician obtained and stored the data electronically at a pre-programmed form within the clinical information system. The data of this initial cohort was prospectively obtained in the period from March 29, 2007 to April first, 2008.

In our clinical information system, 35 patients from the initial cohort have been registered as deceased in the meantime. The remaining patients of the cohort have been contacted by conventional mail in April 2014 and asked to answer a specific, psychologically elaborated, but not validated, paper-questionnaire (Table I). The paper-questionnaire had a multiple-choice design and could be sent back to us by mail without any charges. However, participation in the survey was voluntary and without any compensation.

The data of this survey cohort was also part of a second study estimating the long-term outcome and satisfaction after the treatment at our ENT department (manuscript submitted).

We directed our attention particularly on following parameters of the patient's medical history: Any recurrent epistaxis episodes, the need for a surgical intervention in order to stop the recurrent bleeding, the patient's history of hypertension and diabetes, and the intake of hemostasis impairing medication now and in the past.

The patient was asked if he or she could recall the initial nosebleed and its treatment. Additionally, he or she was asked whether the initial treatment was performed under general or local anesthesia. The collected data from the paper survey was transferred into a digital format, which then was imported into the statistics software.

We matched these survey answers with the digitally documented protocols in our clinical information system and excluded patients with incongruent data.

The occurrence of a recurrent epistaxis episode during the long-term observation and the surgical intervention at a recurrent episode were defined as primary endpoints.

The statistical analyses were performed by the Statistical Package for the Social Sciences software (SPSS) version 22.0.0.1 (IBM Corp., Armonk, NY, USA).

We performed descriptive statistical analyses and cross-tabulating Pearson Chi-Square tests with asymptotic two-sided significances to evaluate differences in the captured characteristics between the patients group with or without recurrent epistaxis. Binary logistic regression was conducted with recurrent bleeding as dependent variable and following factors as covariates: Sex, age, intake of hemostasis impairing medication: ASA (Acetylsalicylic Acid), Marcoumar® (Phenprocoumon), Plavix® (Clopidogrel), other; patient's history of hypertension and diabetes. We performed the Hosmer-Lemeshow test, which is an evaluated test to determine the goodness of fit of the logistic regression model. Confidential interval for the exponentiation of the B coefficient - Hazard Ratio - was defined as 95%. Results were considered statistically significant at the p-level <0.05.

The study was conducted in accordance to the latest version of the Helsinki declarations and with the permission of the ethical committee of the canton of Zurich (KEK-ZH-Nr.: 2013-0519, ClinicalTrials.gov-Identifier: NCT02127554).

Results:

A total of 568 conventional mails have been sent to patients from the initial cohort. 205 mails were returned by the postal service, due to impossible delivery. 28 mails returned with a death notice by the relatives or carer of the patient.

120 patients returned the filled in questionnaire by mail (120/335=35.8%). These 120 patients answering the request originate from the initial cohort. Their data will be labeled as “survey cohort”. Seven patients had to be excluded from the survey cohort because they did not remember the initial treatment. Four patients did remember the treatment incongruently to our clinical information system. These eleven patients were excluded from the study to eliminate other potentially incorrectly remembered data. Additionally, one patient did not answer the survey-question about any recurrent epistaxis episodes and two patients did not answer the survey-question about the actual use of hemostasis impairing medication. Therefore, 106 patients were analysed.

The survey cohort consisted of 68.9% (73) male and 31.1% (33) female patients. This imbalance did not show a significant difference concerning the primary endpoint of a recurrence. The mean interval between the initial cohort and the survey cohort was 76.58 months (SD 4.0 [71 – 84 Mt]). The initial cohort showed the following distribution of hemostasis impairing medication intake: 46.2% (49/106) none, 34.9% (37/106) ASA only, 10.4% (11/106) VKA, 7.5% (8/106) combined antiplatelet therapy of ASA and Clopidogrel, 0.9% (1/106) Clopidogrel only.

The survey cohort showed following distribution of hemostasis impairing medication intake: 49.1% (52/106) none, 36.8% (39/106) ASA, 10.4% (11/106) VKA, 0.9% (1/106) combined therapy of ASA and VKA, 0.9% (1/106) antiplatelet therapy with Clopidogrel, 1.9% (2/106) other. The shift of types of treatment is depicted in Figure 1. Regarding the overall ASA shift in single cases reveals that 17 patients of initially

45 (37.8%) discontinued ASA intake between the initial and the survey time point. In contrast did eleven patients start to take ASA. Of those eleven patients did eight individuals declare no exposure to any antithrombotic medication at the initial cohort, and three individuals declared exposure to a VKA. The need for an adaptation of the VKA therapy or application of Vitamin K in the initial cohort has been published previously[14].

Regarding the overall VKA shift in single cases reveals that three patients of initially eleven (27.3%) discontinued VKA intake between the initial cohort and the survey cohort. In contrast did four patients start to take VKA. Of those four patients did three individuals declare exposure to ASA only at the initial cohort, and one individual declared exposure to the combination of ASA and Clopidogrel.

41.5% (44/106) reported a recurrent epistaxis episode on either side of the nose. Patients that declared intake of a VKA at the survey showed significantly more frequently a recurrent epistaxis episode ($p = 0.002$). 83.3% (10/12) of patients with exposure to VKA suffered from a recurrent episode, while 16.7% (2/12) did not (Table 2).

The binary logistic regression confirmed the intake of VKA as an independent and significant risk factor for a recurrent epistaxis episode with an odds ratio of 11.6 ($p=0.007$) (Table 3). Goodness of fit was confirmed by the Hosmer and Lemeshow test ($p = 0.882$, $Chi^2 = 3.710$).

No further covariate, including any other hemostasis impairing medication, showed significance as an independent risk factor for a recurrent epistaxis episode.

19 of the 44 patients (43.2%) suffering from a recurrent bleeding declared treatment of a subsequent episode by an ENT specialist. Eleven (11/19=57.9%) patients have sought an ENT specialist in a private practice and reported following distribution of

225 epistaxis treatment: Eight (8) coagulations, one (1) packing, one (1) packing with
226 subsequent coagulation and one (1) did not reported the performed treatment.
227 Eight (8/19=42.1%) patients have sought our tertiary ENT emergency and reported
228 following distribution of epistaxis treatment: Two (2) coagulations, Two (2) packings,
229 one (1) packing with subsequent coagulation, one (1) packing with subsequent
230 surgical intervention and two (2) surgical interventions only.
231 Every single patient (3/3) who had to undergo a surgical intervention in order to stop
232 a recurrent bleeding stated ASA intake at the initial time point.
233
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Discussion:

This cohort survey study is able to show that the intake of a VKA is a significant and independent long-term risk factor for recurrent epistaxis episodes, while ASA did not exert a significantly increased risk for recurrent episodes in a long-term perspective. The exposure to acetylsalicylic acid did however show a link to severe recurrent nosebleeds, with the need of a more invasive therapeutic revision-intervention.

An extrapolated calculation estimated a prevalence of 15.8% for minor recurrent epistaxis episodes.[4] In our cohort the recurrence rate was very high with more than every third patient suffering from a recurrent episode. Several potential risk factors for epistaxis have been identified and discussed controversially for many years. Some proposed factors maintained their position, and others were either pushed into the background or were able to gain more attention.

Examples for evaluated risk factors are traumatic injury, physical and chemical irritation, allergic rhinitis, viral and bacterial rhinosinusitis, nasal tumors, temperature and humidity or hemostasis impairment. [5,6] Examples for non fully confirmed but discussed potential risk factors are hypertension[7], alcohol consumption[8], septal spurs or deviation.[9]

A study, conducted to investigate short-time recurrences showed treatment with untargeted gauze packing due to an unidentified bleeding source as a significant risk factor for a subsequent bleeding within a one week timeframe.[10] On the contrary, did other concurrently observed risk factors, i.e. patient's history for rhinitis or sinusitis, septal deviation, use of antithrombotic agents or history for hypertension show no significant differences.[10] An investigation about the effectiveness of different treatment options in epistaxis endorsed that coagulation at an anterior and surgical occlusion at a posterior bleeding are able to successfully salvage failed packing

therapies.[11] Therefore is the appropriate choice of a treatment option of essential importance in order to reduce recurrences.

Vitamin K antagonist therapy is a long-standing and widely postulated risk factor for epistaxis.[12] A recent, retrospective and controlled cohort study endorses the suggestions and showed, that besides the exposure to Warfarin®, none of the widely believed risk factors for epistaxis in general, were associated with risk of recurrence during a three years period.[13]

This is in accordance with our finding of Marcoumar®, a Europe-wide used VKA, as an independent long-term risk factor for recurrent epistaxis episodes. Exposure to VKA, especially if not regularly checked by a physician, can easily lead to INR levels that are too high. In order to take appropriate action in case of a nosebleed in patients who are not within optimal target value ranges, it is recommended to test the prothrombin time and INR in every epistaxis patient on VKAs.[14]

The intake of acetylsalicylic acid has recently been added to the group of risk factors. Although already proposed as a risk factor in the last millennium[15], it has unjustly been pushed into the background by the VKA. Recently, it has been reasserted that antiaggregational therapy with ASA is not only a subsidiary but a major risk factor for epistaxis and a higher severity.[3] In the same study, did the exposure to ASA supersede VKA therapy as a risk factor for severe epistaxis.

To the best of our knowledge does the current literature not address the long-term course of epistaxis patients during a timeframe of more than three years as done in our investigation.

The exposure to VKA compared to other antithrombotic agents and potential risk factors shows an odds ratio of 11.6 for recurrences. We also could support the finding of exposure to ASA as a risk factor for epistaxis episodes with high severity not only in a short- but also in a long-term perspective. Therefore, for patients with

exposure to ASA an increased probability for a surgical intervention in order to stop a recurrent bleeding can be predicted. This finding is not statistically significant due to its small number of cases. Nonetheless did all patients that required a surgical intervention in order to stop a recurrent bleeding declare ASA intake at the initial cohort.

Hypertension as a potential risk factor[7] is still controversially discussed and not confirmed. It was repeatedly described not to increase the risk for epistaxis or its severity.[3,16] Acute hypertension during a nosebleed is a proposed[17] and intuitively apparent cause for a refractory epistaxis. Nevertheless, was acute hypertension counter-intuitively not a risk factor for severe epistaxis in our own analysis of almost 600 emergency events.[3] On the long run, hypertension appears to be a weak proximate risk factor, as only a (non-significant) trend was observed towards more recurrences. In addition to hypertension, the covariate male sex also showed an independent statistical trend for an increased risk for epistaxis. It has been confirmed that men are at risk for a more extensive coronary disease compared to women.[18] These findings support the idea that atherosclerosis, as a consequence of long-term hypertension and thus continuous stress to the vascular system, leads to more vulnerable vessels and thus bleeding and recurrences.[19]

The study is limited due to its non-controlled design and a relatively low response rate of 35.8% (120/335). However, in such a long postinterventional timeframe and a relatively old population this was anticipated and therefore a high number of more than 500 patients in a mean timeframe of 76 months was chosen in order to get the lowest possible bias. A further potentially limiting factor could be a selection bias. We consider a selection bias as unlikely, since our cohort was large and there was no obvious bias concerning the responders and non-responders.

In contrast to other studies, we also acquired minor epistaxis episodes, which are defined as episodes that were handled autonomously by the patient without seeking help of a general practitioner or an ENT specialist. Therefore, we collected recurrent episodes regardless of their severity and thus included a cohort that most likely represents a very representative group of epistaxis patients. Furthermore, the Hosmer and Lemeshow test indicated a good fit of our logistic regression model.

Conclusion:

Recurrent bleedings after epistaxis treatment are underestimated and occur at a very high rate. We provide evidence that the intake of a VKA is an independent long-term risk factor for recurrent epistaxis episodes.

The intake of ASA is a risk factor for the severity of recurrent epistaxis episodes with the increased need for a surgical intervention not only in a short- but also in a long-term perspective.

Concerning the above mentioned increased risks, we recommend prescribing both antithrombotic agents only with an indisputable indication. In line with our previous studies we imperatively discourage from taking ASA as a “lifestyle drug” at any age. However, further studies are needed to endorse this recommendation.

Patients with a high-risk profile should be informed and trained in the prevention, first-aid measures and then seeking medical advice in case of recurrent epistaxis. Therefore, in order to assess the patients’ risk profile and to provide an accurate prognosis it is once again crucial to meticulously record the patients’ history. Matching the patient’s history with evaluated epistaxis risk factors leads to a better counseling concerning recurrent episodes or their severity.

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Table 1

Specific, psychologically elaborated, but not validated, paper-questionnaire

1. Do you remember the treatment from xxx?
    a. No
    b. Yes
2. Was surgery in general anesthesia needed at the time?
    a. No
    b. Yes
3. Were any of the treatments back then painful for you?
    a. No
    b. Little
    c. Medium
    d. Strong
    e. Very strong
4. Were any of the treatments back then particularly uncomfortable for you?
    a. Cautery
    b. Packing
    c. Surgery
    d. None
5. Have you experienced any complications or lasting sequelae during the treatment or later on?
    a. No
    b. Nasal obstruction
    c. Crusting
    d. Other:
6. Do you suffer from permanent sequelae after the treatment?
    a. No
    b. Yes:
7. Have you experienced nose bleeding after the treatment?
    a. No
    b. Yes, which side?
    c. How many times a year?
8. Did you need medical treatment after the initial event?
    a. No
    b. Yes
    c. When?
    d. Where?
9. What was done?
    a. Cautery
    b. Packing
    c. Surgery
10. Do you take anticoagulant medication?
    a. No
    b. Aspirin
    c. Marcoumar® (Phenprocoumon)
    d. Plavix® (Clopidogrel)
    e. Other:
11. Do you have a high blood pressure?
    a. No
    b. Yes
12. Do you take any medication because of your blood pressure?
    a. No
    b. Yes
13. Do you have an elevated blood glucose level (Diabetes)?
    a. No
    b. Yes
14. Are you treated because of your blood glucose (Diabetes)?
    a. No
    b. Yes
15. In case of recurrent nosebleed, would you prefer nasal packing without anesthesia or surgery with general anesthesia to stop the bleeding?
    a. Packing without anesthesia
    b. Surgery in general anesthesia

Table 2

Variables stratified by the incidence of a recurrent epistaxis episode. Pearson Chi-Square tests with asymptotic two-sided significances

Variables	Recurrent epistaxis (n = 44)	No recurrent epistaxis (n = 62)	*p* Value
VKA (Marcoumar®)	10	2	.002
ASA	14	26	.290
Clopidogrel	1	0	.233
Other antithrombotic medication	1	1	.806
Sex			.115
- Male	34	39	
- Female	10	23	
Mean age at the initial event (SD), years	62.94 (16.02)	63.37 (15.67)	.889
Patient's history for hypertension	31	32	.052
Patient's history for diabetes	5	4	.371

Abbreviation: SD, standard deviation

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Table 3

Binary Logistic Regression with epistaxis recurrence as dependent variable.

Covariates	*p* Value	OR	95% CI for OR	
			Lower	Upper
VKA (Marcoumar®)	.007	11.587	1.973	68.057
ASA	.607	.780	.304	2.005
Clopidogrel	1.000	>10	.000	.
Other antithrombotic medication	.682	1.856	.096	35.717
Sex	.072	2.549	.919	7.068
Age at the initial event	.247	.982	.952	1.013
Patient's history for hypertension	.086	2.397	.884	6.500
Patient's history for diabetes	.373	2.062	.419	10.146

Abbreviations: CI, confidential interval; OR, odds ratio

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Figure legends:

Figure 1: Shift of ASA (Acetylsalicylic Acid) and VKA (vitamin K antagonist) intake between the initial cohort and the survey cohort; y-axis: 0 to 100 patients.